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TOPICAL HAZARD EVALUATION OF CANDIDATE INSECT REPELLENT AI3-365--ETC(U)
MAY 77 M H WEEKS, B J DESENA

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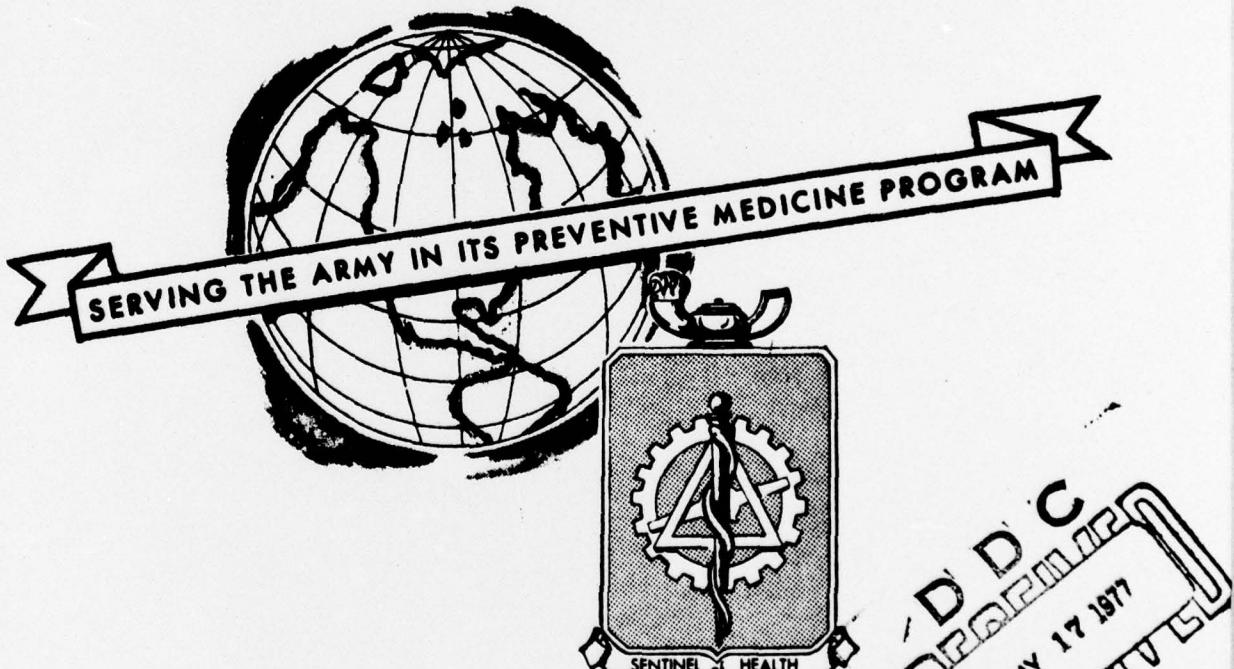
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TOPICAL HAZARD EVALUATION
OF CANDIDATE INSECT REPELLENT AI3- 36539
1-(CYCLOHEXYLCARBONYL)-2-ETHYLPIPERIDINE
STUDY NO. 51-0816-77
OCTOBER 1975 - DECEMBER 1976

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ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MD 21010

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ABERDEEN PROVING GROUND, MARYLAND 21010

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ABSTRACT

A hazard evaluation of AI3- 36539 was conducted using New Zealand White rabbits for skin and eye studies and Hartley guinea pigs for a skin sensitization study. Technical grade compound caused in rabbits moderate to severe skin irritation, and mild injury to cornea with some injury to the conjunctiva of the eyes. Ethanol solutions of AI3-36539 caused primary skin irritation and may be irritating to the skin of man. Based on these findings, it is recommended that AI3- 36539 not be approved for further testing as a candidate topical insect repellent. However, should the insect repellent qualities indicate that it presents a substantial improvement over standard repellents, it should be resubmitted in the form and concentration intended for usage.

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1-(CYCLOHEXYLCARBONYL)-2-ETHYLPIPERIDINE
STUDY NO. 51-0816-77
OCTOBER 1975 - DECEMBER 1976

1. AUTHORITY.

a. Letter, US Department of Agriculture, Agricultural Research Service, Southern Region, Insects Affecting Man Research Laboratory, Gainesville, FL, 17 October 1975.

b. Memorandum of Understanding Between the US Department of the Army, Office of The Surgeon General, the US Army Health Services Command, the US Army Environmental Hygiene Agency, the Armed Forces Pest Control Board and the US Department of Agriculture, effective December 1970 with Amendment No. 1, effective August 1974.

2. REFERENCE. Toxicology Division Procedural Guide, US Army Environmental Hygiene Agency (USAEEHA), 1972.

3. PURPOSE. The purpose of this study was to provide guidance for further entomological testing of the candidate insect repellent AI3- 36539.

4. SUMMARY OF FINDINGS. A hazard evaluation of the candidate repellent AI3-36539, 1-(cyclohexylcarbonyl)-2-ethylpiperidine, was conducted by this Agency using New Zealand White rabbits for skin and eye studies and Hartley guinea pigs for a skin sensitization study. A tabular presentation of animal toxicity data developed in this Agency follows:^{*†}

^{*}In conducting the studies described in this report, the investigators adhered to the "Guide for Care and Use of Laboratory Animals," US Department of Health, Education and Welfare Publication No. (NIH) 74-23, revised 1972 - second printing 1974.

[†]The experiments reported herein were performed in animal facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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TABULAR PRESENTATION OF DATA

Test	Results	Interpretation
<u>SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application to intact and abraded skin of New Zealand White rabbits.	AI3-36539 produced well defined and moderate-to-severe erythema in six of six rabbits and slight edema in four of six rabbits at 24 and 72 hours following application.	USAEHA Category III (ref Appendix)
0.5 ml technical grade compound applied to each of six rabbits.	No signs at 7 days.	
<u>EYE IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application of 0.1 ml technical grade compound to one eye of each of six New Zealand White rabbits.	AI3-36539 produced mild injury to the cornea and, in addition, some injury to the conjunctiva.	USAEHA Category C (ref Appendix)
	No signs at 7 days.	
<u>SENSITIZATION STUDIES</u>		
<u>Guinea Pigs (Male)</u>		
Intradermal injections of 0.1 ml of a 0.1 percent suspension (w/v) of AI3-36539 or dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.		

*A known skin sensitizer.

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Test	Results	Interpretation
Ten test guinea pigs received and challenged with 0.1 percent suspension of AI3-36539.	Challenge dose of test compound (last intra-dermal injection) did not produce a sensitization reaction.	Compound AI3-36539 did not produce a sensitization reaction under test conditions and is not expected to produce a sensitization reaction in man.
Ten positive control guinea pigs received and challenged with 0.1 percent suspension of DNCB.	Positive control (DNCB) produced a marked sensitization reaction in ten out of ten guinea pigs.	
Ten cage control guinea pigs; five receiving challenge dose of test compound without prior sensitizing doses; five receiving challenge dose of DNCB without prior sensitizing doses.	Cage control guinea pigs showed no greater reaction to test compound and DNCB than were seen in original test groups.	

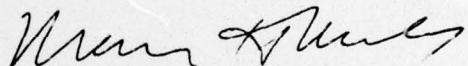
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Test	Results	Interpretation
<u>PHOTOCHEMICAL SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
A single application (0.05 ml) of a 25 percent (w/v) solution of the compound and of a 10 percent (w/v) oil of Bergamot solution (positive control) in 95 percent ethyl alcohol, were applied to the intact skin of six New Zealand White rabbits. Five minutes after application, the rabbits were exposed to UV light (365 nm) for 30 minutes from a distance of 10 to 15 cm.	AI3-36539 did not cause a photochemical skin irritation reaction under test conditions. However, ethanol solutions of AI3-36539 caused the same degree of moderate to severe erythema and edema at both irradiated and non-irradiated skin sites.	Although AI3-36539 was not a photochemical skin irritant, ethanol solutions of this compound were primary skin irritants and may cause a similar skin reaction in man.
<u>Control</u>		
Following UV exposure of the rabbits, 0.05 ml of the test compound positive control, and diluent were applied to additional skin areas to serve as unirradiated control sites.	Positive control (oil of Bergamot) application and irradiations caused greater irritant effects than in un-irradiated areas.	
Application areas were checked for irritation at 24, 48 and 72 hours.		

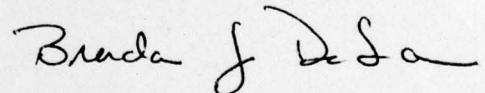
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5. CONCLUSION. Single applications of the technical grade compound caused in rabbits moderate-to-severe skin irritation, mild injury to the cornea and some irritation to the conjunctiva. Ethanol solutions of AI3-36539 produced moderate-to-severe erythema and edema at both UV irradiated and non-irradiated rabbit skin sites and may cause a similar adverse skin reaction in man.

6. RECOMMENDATIONS. Under the provisions of the Memorandum of Understanding (reference paragraph 1b), it is recommended that AI3-36539 not be approved for further testing as a candidate topical insect repellent. However, should the insect repellent qualities indicate that it presents a substantial improvement over standard repellents, it should be resubmitted in the form and concentration intended for usage.



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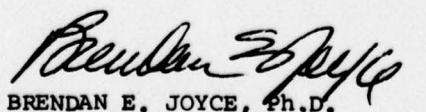


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APPENDIX

TOPICAL HAZARD EVALUATION PROGRAM
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING
CONSIDERED FOR ACUTE SKIN APPLICATION

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion! (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals. prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

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C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.